DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service
Food and Drug Administration
Rockville MD 20857

DATE: May 14, 2008

TO: Randall W. Lutter, Ph.D.
Deputy Commissioner for Policy
Food and Drug Administration

THROUGH: Vince Tolino /s/
Director, Ethics and Integrity Staff
Office of Management Programs
Office of Management

Michael F. Ortwerth, Ph.D. /s/
Deputy Director, Advisory Committee Oversight and Management Staff
Office of Policy, Planning, and Preparedness

FROM: Igor Cerny, Pharm.D. /s/
Director, Advisors and Consultants Staff
Center for Drug Evaluation and Research

SUBJECT: 208(b)(3) Conflict of Interest Waiver for Robert Califf, M.D.

I am writing to request a waiver for Robert Califf, M.D., a Temporary Non-voting Member to the Endocrinologic and Metabolic Drugs Advisory Committee, from the conflict of interest prohibitions of 18 U.S.C. §208(a). Waivers under section 208(b)(3) may be granted by the appointing official where "the need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved" and where the individual has made a disclosure of the financial interests at issue. We have determined that you are the appointing official for purposes of section 208. Therefore, you have the authority to grant Dr. Califf a limited waiver under section 208(b)(3).

Section 208(a) prohibits Federal executive branch employees, including special Government employees, from participating personally and substantially in matters in which the employee or his employer has a financial interest. Because Dr. Califf is a special Government employee, he is under a statutory obligation to refrain from participating in any deliberations that involve a particular matter having a direct and predictable effect on a financial interest attributable to him or his employer.

The function of the Endocrinologic and Metabolic Drugs Advisory Committee is to review and evaluate available data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of endocrine and metabolic disorders and to make appropriate recommendations to the Commissioner of Food and Drugs.

Dr. Robert Califf has been invited to present and answer questions regarding the "Challenges in Designing a Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes" in the July 1-2, 2008, meeting. The committee will discuss the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus.

This matter is coming before a meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. This issue is a particular matter involving specific parties.

Dr. Califf has advised the Food and Drug Administration that he has financial interests that could potentially be affected by his participation in the matter at issue. Dr. Califf is the Vice Chancellor for the Clinical Research and Director of the Duke Translational Medicine Institute (DTMI) at Duke University Medical Center. In 2007, Dr. Califf became the Principal Investigator of the Clinical and Translational Science Award from the National Institutes of Health (NIH), which has provided major institutional support to create DTMI. Dr. Califf' is in a role to oversee a broad portfolio of research that includes funding from NIH, Agency for Healthcare Research and Quality (AHRQ), Department of Defense (DOD), multiple foundations and industry. For his involvement in trials, all payments to Dr. Califf are made through a research contract with Duke University, and his efforts are reflected on his effort report for the university, which oversees the academic freedom important to Dr. Califf's conduct of duties in generating evidence for clinical practice.

DTMI was awarded research grants by ——— to conduct the ——————— Study of ——————————————in the prevention of ——————————————— in subjects with ——————————— funded by ———. Dr. Califf is the Principal investigator. The trial commenced in ——————and follow-up is now ongoing and will finish up in the next 18 months. DTMI is not the coordinating center for this trial but the funding partly goes to pay for his salary and also supports a junior faculty member who assists with trial leadership.

Duke University Medical Center and Dr. Califf are finalizing plans for the conduct of a global trial of the cardiovascular safety of ————————————. Dr. Califf will be the Co-Principal Investigator for the study. Enrollment will commence in September or October 2008.

Dr. Califf also discussed the potential for an outcomes trial on ——————————— with ——————. Dr. Califf has no knowledge of the anticipated study dates or potential funding at this point and there has been no financial transaction associated with the brief discussions.

In addition, Dr. Califf will be consulting with——— on a trial assessing the impact of ——————— ——— on cardiovascular events. The first meeting is anticipated to be in late May 2008. All consulting income is donated to non-profit organizations, with the majority going to the clinical research fellowship fund of the Duke Clinical Institute. Also, Dr. Califf is a consultant to ——— and serve on their ——————————————, which is a group of leaders who evaluate the ——— portfolio in cardiovascular and metabolic diseases. All consulting income is donated to non-profit organizations, with the majority going to the clinical research fellowship fund of the Duke Clinical Institute.

———, ——, ————————, and ——— are affected firms of this meeting.

In addition, Dr. Califf's employer, DTMI, has current unrelated contracts with ———, ————————, ———, ————————, and ———. Dr. Califf was a consultant to ————————in the past. Arguably, these unrelated contracts and past consulting work do not constitute a financial interest in the matter under 18 U.S.C. § 208(a).

As a Temporary Non-voting Member of the Endocrinologic and Metabolic Drugs Advisory Committee, Dr. Califf potentially could become involved in matters that could affect his financial interests. Under section 208, he is prohibited from participating in such matters. However, as noted above, you have the authority under section 208(b)(3) to grant a limited waiver permitting Dr. Califf to present and answer questions regarding the "Challenges in Designing a Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes." He will not be allowed to participate in any of the committees' discussions, deliberations, or voting with respect to the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus.

For the following reasons, I believe that it would be appropriate for you to grant a limited waiver to Dr. Califf that would allow him to participate partially in the matter described because the need for his services greatly outweighs the conflict of interest created by these financial interests.

First, although Dr. Califf currently has consulting activities planned with ——— and ————, he has a wide variety of other unrelated consulting activities with many companies. Only a modest fraction of his overall activities is on behalf of any single company. To further mitigate his consulting interest, Dr. Califf donates all the fees received from pharmaceutical companies to non-profit organizations, with the majority going to the clinical research fellowship fund of the Duke Clinical Institute.

Second, although Dr. Califf's employer has current and prospective financial interests in potentially affected firms, these are not personal interests but are imputed to him. Generally, there is less likelihood that the judgment of the individual will be affected by an imputed interest of an employer than by a personal financial interest. Even if it were possible that these firms would be more or less likely to continue to provide financial support to the Duke University Medical Center in the future as a result of the committees' deliberations, the financial impact would probably be relatively insignificant since these are not significant financial interests. Duke University Medical Center is a large, diverse, research institution that receives funding from a variety of public, private, and governmental agencies in support of its research activities. It does not depend upon one or two sources for its funding. It is unlikely that the funding from ————,———, and ———————— represents a substantial portion of the center's total research budget. In 2005, the Duke University Medical Center received over $————in funding from a variety of public, private, and governmental agencies in support of its research activities.

Third, according to the Review Division, the uniqueness of Dr. Califf's qualification justifies granting this waiver. Over the past few years, and recently after the rosiglitazone issue, there has been much public debate surrounding the need for cardiovascular outcomes data for an anti-diabetic agent. The debate is quite divided with advocates for such data arguing that requiring such studies will improve knowledge on the efficacy and safety of a drug. Critics of such a position have argued that the requirement of such costly clinical trials would slow down the availability of effective therapies targeting treatment of hyperglycemia, a surrogate that has direct impact on

other complications in diabetes aside from cardiovascular risks. It is important to note that treatment of diabetes targets normal glycemic control to reduce many risks, microvascular and macrovascular. Over the past several decades, evidence that good glycemic control reduces the risk of microvascular complications such as kidney failure, blindness, and neuropathy is extensive from several large clinical trials.

Of recent, several individuals have publicly called for the conduct of cardiovascular outcomes trials in the evaluation of anti-diabetic drugs. It is not clear whether these individuals understand what it takes to conduct such a trial to casually assert that this is feasible with every anti-diabetic drug. In fact, this is one of the driving reasons for holding this advisory committee to inform the public of these matters.

As a clinical trialist and a cardiologist who has had firsthand experience in many different roles and responsibilities in the conduct of large cardiovascular outcomes trials, it is without doubt that he is the best qualified to speak at this advisory committee meeting for the topic titled, "Challenges in Designing a Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes". Dr. Califf will not only recognize the economic burden of these trials but more importantly he will be able to inform the committee members to the magnitude of site recruitment, investigator selection and personnel training, working with Institutional Review Boards, patient recruitment, selection, and retention. Most notable is Dr. Califf's vast experience with conducting clinical trials internationally. In this day and age, it is highly unlikely that clinical cardiovascular outcomes trial will only take place within the boundaries of the United States or North America. Dr. Califf has been specifically selected to speak at this meeting because of his extensive experience with implementing and executing trials within the United States and throughout the world. Advisory committee members will need to be informed of this fact and inquire of Dr. Califf the potential impact of foreign studies or foreign sites embedded within a clinical trial as it deliberates on whether cardiovascular outcomes trials should be a requirement in the approval of anti-diabetic drugs.

It should be emphasized that Dr. Califf is not being called upon to speak about one particular trial. Other speakers will cover results of previously conducted studies and studies that are ongoing in the diabetic patient population. Dr. Califf is being asked to focus on the "challenges of trial design" in general and will not be given the opportunity to campaign or call for support for any investigations he is directly involved in.

Lastly, locating qualified individuals without disqualifying financial interest to serve on this advisory committee has been very difficult. Dr. Califf is invited as a speaker only, not a participant in the meeting. The topic of discussion is cardiovascular risk assessment in the approval process for anti-diabetic agents. This meeting touches not only on the approval of therapies for diabetes management but on cardiovascular risk in this patient population, interventions to reduce this risk, and complex study designs. As such, the meeting will require the participation of a multi-disciplinary committee including endocrinologists/diabetologists, cardiologists, and biostatisticians. The Division reviewed Special Government Employees (SGEs) from the Cardiovascular and Renal drugs advisory committee and several of these members have already been invited to serve as committee members for this meeting. However, only two SGEs have the expertise as clinical trialists in cardiovascular outcomes trials to provide expert presentations as

speakers to the committee members. The other speaker who has expertise in cardiovascular outcomes trials also requires a waiver to present during the meeting.

Moreover, the Federal Advisory Committee Act requires that committee memberships be fairly balanced in terms of the points of view represented and the functions to be performed by the advisory committee. Also, the committee's intended purpose would be significantly impaired if the agency could not call upon experts who have become eminent in their fields, notwithstanding the financial interests and affiliations they may have acquired as a result of their demonstrated abilities. Dr. Robert Califf is Professor of Medicine and Associate Vice Chancellor for Clinical Research at the Duke Clinical Research Institute. He has training in internal medicine and cardiology and has held numerous prestigious positions in medical societies, scientific organizations, government and industry. He has had extensive experience in conducting large cardiovascular outcomes trials across many different roles including as a principal investigator, a data safety monitoring board member, a Steering Committee member, and an adjudicator of endpoint events.

In addition, any conflict or appearance of a conflict will be mitigated further by our recommendation to limit Dr. Califf's participation to presenting and answering questions regarding the "Challenges in Designing a Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes." Under the terms of this limited waiver, he will not be allowed to participate in the committees' discussions, deliberations, or voting with respect to the discussions on the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus.

Accordingly, I recommend that you grant Robert Califf, M.D., a limited waiver that will permit him to present and answer questions regarding the "Challenges in Designing a Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes." I believe that such a limited waiver is appropriate because in this case, the need for the services of Dr. Califf outweighs the potential for a conflict of interest created by the financial interests attributable to him.

DECISION:

X Limited waiver granted (limited to presenting and answering questions) based on my determination, made in accordance with section 208(b)(3), that the need for the individual's services outweighs the potential for a conflict of interest created by the financial interest attributable to the individual.

___ Waiver denied.

/s/ 6/13/08

Randall W. Lutter, Ph.D. Date
Deputy Commissioner for Policy
Food and Drug Administration